IJBHTM

ISSN: 0975 3893
IJBHTM (2010), 2(2):5-10

Diabetes: Techniques for Blood Glucose Measurement -A Review

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ABSTRACT
Diabetes is a major worldwide health problem prompting to markedly increase cardiovascular mortality and morbidity. The incidence of diabetes mellitus is assuming epidemic proportions in the developing countries. Due to increasing obesity, sedentariness and dietary habits in developing countries, the prevalence of diabetes is growing at an exponential rate. Modern hypoglycemic agents and self monitoring blood glucose (SMBG) sensors are available for the treatment/diagnosis of diabetes. Problems with SMBG devices include the requirement for a drop of blood for each test (usually obtained from a finger). The blood sampling can be painful. Hence we need alternative noninvasive techniques to measure the blood glucose level in diabetic patients. This review article gives information about diabetes mellitus along with role of modern hypoglycemic agents, self monitoring glucose sensors and technology based noninvasive methods for the measurement of blood glucose and is particularly helpful for village population.

Key words: Diabetes, hypoglycemic agents, glucose sensor, noninvasive methods, glucose measurement

INTRODUCTION

Diabetes mellitus is a chronic disease characterized by abnormal insulin secretion, derangement in carbohydrate and lipid metabolism. Insulin hormone is produced in pancreas which enables body cells to absorb glucose, to turn into energy. When glucose is not absorbed by the body cells, it gets accumulated in the blood. This is said to be hyperglycemia [1, 2]. Diabetes is known to the human beings many years ago mainly from prehistoric times. Diabetes was first identified by Egyptians about 3500 years ago. Diabetes was given its name by the Greek Physician Aretaeus. He recorded a disease with symptoms such as constant thirst (polydipsia), excessive urination (polyuria) and loss of weight. He named the condition 'diabetes', meaning 'a flowing through'. In 1870s, a French physician discovered a link between diabetes and diet intake. Due to this reason, formulation of individual diet plan came into picture. Diabetic diet was formulated with inclusion of milk, oats and other fiber containing foods. Function of insulin**,** its nature, along with its use started from 1920 -1923 and discovered by Dr. Banting, Prof. Macleod and Dr .Collip. They were awarded a Noble prize for this discovery. In the decade of 1940, it has been discovered that different organs like kidney and skin are also affected if diabetes is creeping from a long term. Diabetes was recognized with complete details and its types (Type 1 diabetes (insulin dependent) and Type 2 diabetes (non insulin dependent) in the year of 1959. Scientists are continuously working to relieve patients from diabetes, by discovering the relevant drugs [3, 4].

CLASSIFICATION OF DIABETES

Type 1 diabetes

Type 1 diabetes occurs due to autoimmune destruction of insulin-producing beta cells of the pancreas, rendering the pancreas unable to synthesize and secrete insulin. The symptoms of the type 1 diabetes are polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger) and loss of body weight. Type 1 diabetes affects 5 to 10% of the people. In type 1 diabetes, insulin is required for the survival and to prevent the development of ketoacidosis and coma. Type 1 diabetes can occur in any age though common in young individuals [5, 6]. Other symptoms of type 1 diabetes are thirst feeling, often urination, losing weight without trying, having tingling or losing the feeling in the feet and blurry eye sight.

Type 2 Diabetes

Type 2 diabetes is most common and is characterized by combination of insulin resistance (physiological condition in which insulin becomes less effective in lowering the blood sugar level) and inadequate insulin secretion. Type 2 diabetes affects 90 to 95% of people. The major symptoms of type 2 diabetes are polydipsia, polyuria, polyphegia, blurry vision, fatigue and irritability. Type 2 diabetes occurs mainly due to nurture and nature. The external factors are sedentary habits, inappropriate diet and obesity. In addition, mutation of pancreatic cells may occur in type 2 diabetes [7, 8].

Gestational diabetes

Gestational diabetes is form of diabetes which affects pregnant women. It is believed that the hormones produced during pregnancy reduce the woman's receptivity to insulin, leading to high blood sugar level. Gestational diabetes affects 4% of pregnant women. The symptoms of gestational diabetes are fatigue, nausea, vomiting, increase urination, bladder infections and blurred vision. Gestational diabetes may be a temporary phase; it may disappear after pregnancy [9].

Genetic defects in beta-cell function

This has been characterized by onset of mild hyperglycemia at an early age presumably before age of 25 years. This type of diabetes typically inherited in an autosomal dominant pattern. Patients with these form of diabetes referred to as Maturity Onset Diabetes of Young (MODY). Inability in conversion of pro-insulin to insulin due to the genetic abnormalities may also results in diabetes [10].

Diabetes complication

Diabetic complications occur due to high blood sugar level with instability in the hormones. Diabetes may lead to higher risk of heart disease, bone and joint disorders. Problems with teeth, gums, sexual dysfunction and digestive problems are some diabetic complication [11].

- Diabetic retinopathy- It shows symptoms of pain in the eyes and may result in loss of vision.
- Autonomic neuropathy- nerves controlling internal organs get damaged. Example digestive problem.
- Chest pain- angina may occur.
- Some other symptoms- Tingling, burning, shooting or stabbing pain in the hands or other parts of the body, profuse sweating, difficulty to sense the fullness of urinary bladder. When low blood sugar arises, increased sexual problems, weakness, dizziness and fainting etc. may occur.

TESTS USED FOR DIAGNOSIS OF DIABETES

Fasting plasma glucose (FPG) test:

The fasting plasma glucose (FPG) test measures blood sugar levels and is used to diagnose diabetes. Relatively simple and inexpensive, the test exposes problems with insulin functioning. It is most reliable test when done in the morning. People with a fasting glucose level of 100-125 milligrams per deciliter (mg/dL) have a form of pre-diabetes called impaired fasting glucose (IFG). A level of 126 mg/dl or above is confirmed by repeating the test on another day to confirm the diabetes [12].

The results are predicted as:

Plasma glucose level is 99mg/dl or below → diagnosed as normal.

Plasma glucose level is 100-125 mg/dl → diagnosed as pre-diabetes.

Plasma glucose level is 126 mg/dl → diagnosed as diabetes

Oral glucose tolerance test (OGTT)

The test will be done two times. First test is done to the patient fasting for at least 8 hours and the second test is done to the patient 2 hours after drinking a glucose-containing beverage containing 75 grams of glucose dissolved in water. It is used to diagnose both pre-diabetes and diabetes [13].

Results are predicted as:

Plasma glucose level is 139 mg/dl and below → diagnosed as normal.

Plasma glucose level is 140-199 mg/dl → diagnosed as pre-diabetes

Random plasma glucose test

Random plasma glucose test also called as casual plasma glucose test. It is used to diagnose diabetes along with an assessment of symptoms. But pre-diabetes diagnosis is not done. The results have to be confirmed by performing the second test on a different day [14]. A random, or casual, blood glucose level of 200 mg/dl or higher, plus the presence of the following symptoms, can mean a person has diabetes,

- increased urination
- increased thirst and unexplained weight loss

Gestational diabetes detection

Diagnosis has been done based on plasma glucose values. The test is done during pregnancy period, preferably by using 100 grams of glucose in liquid. Blood glucose levels are tested four times during the test. If the test result showed glucose level as above the normal level for two times while performing the test then the women has gestational diabetes [15].

DRUGS USED FOR THE TREATMENT OF DIABETES

Sulphonylureas: It primarily stimulates the pancreatic insulin secretion that in turn reduces hepatic glucose output and increases peripheral glucose disposal. They are classified into first generation and second generation sulphonylureas.

First generation sulphonylureas

a) Acetohexamide
b) Chlorpromide
c) Tolazamide
d) Tolbutamide

Second generation sulphonylureas

a) Glibenclamide
b) Glyburide
c) Glipizide
d) Glicazide

Sulphonylureas

It is also called as insulin secretgouges. They initially stimulate the pancreatic insulin secretion that in turn reduces hepatic glucose output and increases peripheral glucose disposal. They block the potassium channel and allow the influx of calcium to the

ISSN: 0975 3893
IJBHTM (2010), 2(2):5-10

pancreatic beta-islets of langerhans cells. As a result an increased amount of insulin is released. After several months, insulin level in the blood will return to premedication level but the glucose level in the blood will remain in a reduced state. The drug is also having some other functions like, the rate of release of glucose in the blood stream is slowed, they increase the number of insulin receptors on the cell membrane. The second generation sulphonylureas have some advantages than first generation sulphonylureas. Even a small milligram of the drug is more efficient and they have low side effects. Single dose for a day is more effective than second generation that enables the compliance [16].

Biguanidines

The biguanidine drugs were introduced in 1957. Phenformin and metformin are the two groups of biguanidine. They suppress excessive hepatic glucose production and increased utilization of glucose in the peripheral blood. When they are used alone, they are called as anti-hyperglycemic agents rather than hypoglycemic agents because they do not stimulate endogenous insulin secretion and thus hypoglycemia does not occur. Metformin and phenformin are widely used. Eventhough it may increase the glucose utilization in peripheral cells to a lesser degree by decreasing insulin resistance in muscle cells, they mainly suppress the excessive glucose production. When it is taken alone hypoglycemia will not occur because it does not stimulate endogenous insulin secretion. Hypoglycemia may occur if it is taken along with insulin or sulfonylurea. Metformin have some additional functions like lowering triglyceride and low density lipoprotein (LDL) cholesterol levels while increasing high density lipoprotein cholesterol (HDL). This drug particularly helps type 2 diabetes patients [17].

Alpha-glucosidase inhibitors

Acarbose is an example for alpha-glucosidase inhibitor. It is used in management of post-prandial hyperglycemia. The breakdown of disaccharides, polysaccharides and other carbohydrates to monosaccharide is slowed down by acarbose. The enzymatic generation and subsequent glucose absorption is reduced. Alpha-glucosidase inhibitor does not prevent the absorption of carbohydrates but it delays the process. Lowering of total insulin output of the pancreas, increased insulin sensitivity, mild decrease in triglycerides, less side effects to patients are some of the functions of alpha-glucosidase inhibitors [18].

Thiazolidinediones (TZD)

Increased insulin sensitivity and increased glucose uptake are the primary functions of TZD. The TZD have some effects on hepatic glucose uptake. They will not stimulate pancreas to secrete more insulin. The group has been hepatically metabolized and has minimal side effects. It can be dosed once a day. They have notable effects on lipids. They have minimal effects on LDL, triglyceride and favorable effects on HDL. Rosiglitazone and pioglitazone are approved for monotherapy and are also being used along with metformin and insulin [19, 20].

Self-monitoring blood glucose sensor (invasive monitors)

Testing for urinary glucose began when insulin became available in 1922. This is a non-invasive form of testing but is not a viable option for people with color blindness. Urinary glucose testing also requires access to a toilet which makes it a less practical method [21]. Portable devices for self-monitoring of blood glucose (SMBG) have been developed (Table 1). In current glucose monitors, a drop of blood is placed on a small window in a test strip. Blood glucose acts as a reagent (substance used to measure other substances) in a chemical reaction that produces a color change or generates electrons. Benefit of self-monitoring blood glucose are: maintenance of a specific level of glucose control, prevention and detection of hypoglycemia and avoidance of severe hyperglycemia.

Problems with self-monitoring of blood glucose devices

Invasive monitors provide the most accurate measurements and are comparatively inexpensive. The principle of action of invasive monitors is based on collection of blood sample and its further analysis. The level of glucose in the blood sample is measured using test strips or biosensor. Problems with SMBG devices include the requirement for a drop of blood for each test (usually obtained from a finger). The blood sampling can be painful. However, invasive monitors are inappropriate for continuous monitoring. Therefore; there is a needful to develop non-invasive methods to measure blood glucose level in the diabetic patients.

Demerits of SMBG device

- Collection of blood: Painful
- Inconvenient due to disruption of daily life
- Skin injury

IJBHTM

ISSN: 0975 3893
IJBHTM (2010), 2(2):5-10

Table 1. Blood Glucose Monitors

Glucometer	Manufacturer	Principle	Calibrated for	Sampling Method
Accu-check sensor	Rorche Diagnostics	Sensor	Blood	Sip-in
Accu-check comfort	Rorche Diagnostics	Photometry	Blood	Drop
Accu-check Compact	Rorche Diagnostics	Photometry	Blood	Drop
Glucometer Elite XL	Bayer	Sensor	Plasma	Sip-in
Glucometer Dex 2	Bayer	Sensor	Plasma	Sip-in
One touch sure step	Life scan	Photometry	Plasma	Drop
One touch Profile	Life Scan	Photometry	Blood	Drop
One touch Ultra	Life Scan	Sensor	Plasma	Sip-in
Precision PCx	Abbott/ Medisence	Sensor	Plasma	Sip-in
Precision Xtra	Abbott/ Medisence	Sensor	Plasma	Sip-in
B-Glucose analyzer	HemoCue	Photometry	Blood	Sip-in
GlucoMen	Glyco Menarini	Sensor	Plasma	Sip-in
Omnitest	Braun	Sensor	Plasma	Sip-in

NON-INVASIVE TECHNOLOGY: MEASUREMENTS OF BLOOD GLUCOSE LEVEL

Non-invasive technology include those that do not penetrate into deep layers of tissue where nerve terminals are located, and those with less frequent penetration into those tissues. The advantage of such technologies over the existing ones is less intense and/or less frequent pain while providing acceptable information about the glucose levels. There are some non-invasive methods based on radiation technology.

Advantage of noninvasive technology

- No painful
- Convenient for daily life
- No fear of hypoglycemia
- No skin injury

NON-INVASIVE TECHNOLOGY

- **NIR spectroscopy**
- **Radio wave impedance**
- **Optical rotation of polarized light**

NIR spectroscopy

Near infrared light (NIR) spectroscopy utilizes a source of external light in the infrared spectrum near the visible light that penetrates a body part. Part of the penetrating light is absorbed by glucose. The amount of energy absorbed is analyzed by a technique called spectroscopy and is compared to a detection beam and then is converted into a blood glucose value. The main problems with this technique are the frequent recalibration, the relatively tiny signal absorbed by glucose and the possible absorption of energy by other substances or medications. The body emits thermal radiation. When the energy exits the body, part of it is absorbed by glucose. The absorption in the "glucose band" is related to its concentration. The amount of energy absorbed is determined by spectroscopy and converted to a blood glucose value [22].

Radio wave impedance

Glucose sensing through the use of radio waves is indirect, relying on predictable alterations in how ionic solutes like sodium respond to alternating electromagnetic fields in the presence of glucose. The normal interference in specific radio frequencies caused by sodium is impeded by surrounding glucose molecules. Glucose is not directly affected by longer wavelength radio and microwave frequencies, so its presence cannot be directly measured. But because it is the major solute in a size range close to that of sodium, it generates much of the interference that is seen in sodium's normal impedance pattern glucose could theoretically be measured through this interference pattern. The benefits of radio sensors are that they are painless, require no blood and take just a few seconds to complete. Compared to IR waves, radio waves undergo much less interference and pass readily through the human body, giving much higher transmission rates [23].

Optical rotation of polarized light

The aqueous humor of the eye is the transparent liquid present between the cornea and the iris and its concentration of glucose is proportional to that of the blood. If one applies a beam of infrared polarized light to this solution (the aqueous humor), the beam is shifted by an angle proportionate to the concentration of glucose. This angle can then be converted to a glucose value. Since the concentration of glucose in this tissue is very small, the angle of rotation is also very small and one needs sensitive software to convert this angle into actual blood glucose equivalent [24].

Table 2. Radiation based spectroscopy for measurement of blood glucose level (Noninvasive methods)

Method	Manufacturer	Range (mg/dl)
NIR spectroscopy	Infratech	70-400
Impedance spectroscopy	Pendragon medical	90-250
Optical	Fovi optics	80-400

CONCLUSION

The rate of diabetic prevalence is more in India. Diabetes can be diagnosed by fasting plasma glucose test, oral glucose tolerance test, random plasma glucose test or using self monitoring glucose sensor. For measurement of glucose from fasting blood or by using self monitoring glucose sensor need blood sample from diabetic patients and it will be painful procedure to diagnose the diabetic condition. Many invasive methods and devices are presently available for diagnosis of diabetes. However, noninvasive method for diagnosis of diabetes mellitus is still especially important. A variety of technologies has been developed to diagnosis the diabetes. Some new noninvasive technology such as radiation technology has been developed for diagnosis of diabetes by measuring blood sugar level. Near infrared light (NIR) spectroscopy, Radio wave impedance and optical rotation of polarized light techniques are noninvasive techniques and these has been developed based on radiation technology to diagnose the diabetes or to measure the blood glucose level. The advantages of noninvasive techniques are painless, require no blood and take just a few seconds to complete measurement of blood glucose level. In future, noninvasive techniques may have potential to measure the blood glucose level in the diabetic patients.

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